Cortisone and Corticotropin (ACTH)—A Review

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FOUR YEARS AGO, Hench, Kendall, Slocumb and Polley[51] reported that cortisone and corticotropin (ACTH) effect pronounced and prompt improvement in the signs and symptoms of rheumatoid arthritis. The introduction of two potent agents effective against a disease for which therapeutic agents were sorely lacking was promptly hailed as a major contribution to medicine, but of perhaps greater importance was the demonstration by the investigators that cortisone and corticotropin have a physiologic property, theretofore not generally recognized—the ability to suppress or inhibit inflammatory reaction of mesenchymal tissue, occurring in a variety of diseases. The implications of this discovery have been far-reaching, extending into every field of medicine and surgery. The employment of these hormones in over one hundred disease states has been reported. In some, there apparently has been a rational basis for their use suggested by one or more of their physiologic actions. In others, trial has been purely empiric, justified perhaps by the assumption that these substances may have other physiologic effects as yet undiscovered. An enormous volume of medical literature has appeared incident to these investigations. One published bibliography lists over 3,000 articles which have appeared in less than three years and the list is still growing.[22] The purpose of this review is to select from this enormous literature only a few data on the physiologic and pharmacologic actions of these hormones which appear to be of particular significance to clinicians. For a more comprehensive summary of all adrenocortical steroids and corticotropin the recent series of articles by Thorn and his colleagues is highly recommended.[113]

NATURE OF CORTISONE AND CORTICOTROPIN

Cortisone is a steroid and, like cholesterol, sex hormones and bile acids, contains a phenanthrene nucleus (Figure 1). It was isolated from the adrenal cortex in 1935, and a definite chemical formula assigned to it in 1938 by Kendall and his co-workers.[72] According to Polley and Mason, the significant features of this compound upon which its antirheumatic (and probably anti-inflammatory) properties are dependent are the presence of a ketone group at C-3, a double bond between C-4 and C-5, either a ketone or hydroxyl group at C-11, a ketone group

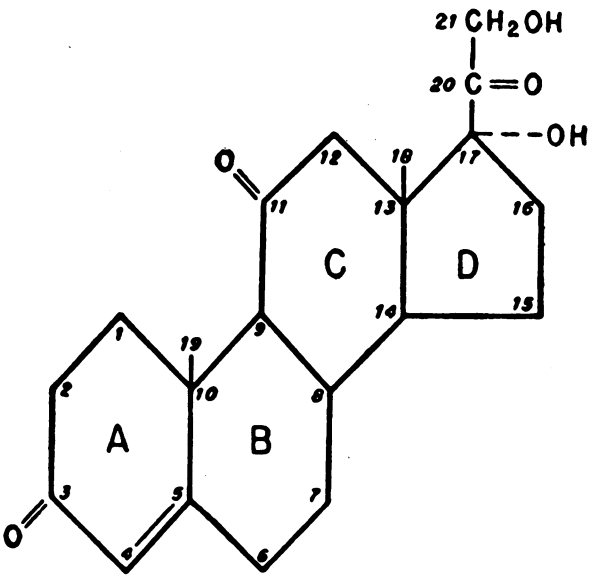

Figure 1.—Chemical formula of cortisone (11-dehydro-17-hydroxycorticosterone or Compound E of Kendall).

at C-20, and hydroxyl groups at C-17 and C-21. The only other steroid that fulfills these criteria is 17-hydroxycorticosterone, or Compound F of Kendall; and it is the only steroid of the many which have been investigated which appears to have significant antirheumatic effect.[90]

Corticotropin is a protein with a molecular weight of approximately 20,000. The hormone has not been isolated in pure form and its chemical formula is not known. Its biologic activity is destroyed by several enzymes, which suggests that one or more peptide bonds are present. It may contain such amino acids as tyrosine, tryptophane and arginine.[6] The studies of Li and Lesh suggested that corticotropic activity may reside in several peptide fractions.[66, 69]

PREPARATIONS

Cortisone is commercially prepared as an acetate ester. The biologic activity of cortisone and cortisone acetate is essentially the same. It is available in 5 mg., 10 mg. and 25 mg. tablets for oral administration, and in a liquid preparation for intramuscular or subcutaneous injection, containing 25 mg. of cortisone in each cubic centimeter. It is also available in a 1.5 per cent ointment and in 0.5 per cent and 2.5 per cent suspensions for ophthalmic use.

Corticotropin is available either as a lyophilized powder in vials containing 10, 25 or 40 provisional U.S.P. units or as a stable solution containing 40 U.S.P. units in each cubic centimeter. A long-acting preparation of lyophilized corticotropin in gelatin is available in 5 cc. vials containing 20 or 40 U.S.P. units in each cubic centimeter. In the past year, a new preparation known as purified corticotropin has become available and will in all probability replace the older long-acting preparation.[80] When administered subcutaneously or intramuscularly, purified corticotropin has a greater clinical effect, unit for unit, than has corticotropin. For convenience, however, the potency of this new preparation is expressed in terms of *clinical activity*, equivalent to a specified number of U.S.P. units of corticotropin, so that a change from corticotropin to purified corticotropin can be made without gross alterations of dose. It is available in 5 cc. vials containing 20 or 40 U.S.P. units in each cubic centimeter.

METHODS OF PREPARATION

The amount of cortisone available by extraction from adrenal glands is exceedingly small. Shortly after the hormone was isolated and its chemical formula ascertained, research began in several laboratories in an effort to produce this hormone synthetically. This was finally accomplished in 1946 by Sarett of Merck Laboratories, using desoxycholic acid derived from beef bile as a starting material.[98] Its preparation is the most complicated procedure in the pharmaceutical laboratory today. Nevertheless, in the past year production has been catching up with the tremendous demand for the hormone. This increased production and presumably competition among various manufacturers has made possible a price reduction to 5 per cent of the cost in 1949.

Corticotropin may be extracted by several methods from hog, sheep and beef pituitary.[5, 70, 99] Astwood and colleagues recently reviewed methods of extraction and purification.[6] Since the chemical formula of corticotropin is unknown, it would seem unlikely that it will ever be produced synthetically. However, there is a possibility that a peptide fraction which appears to have physiologic properties similar to the protein form may some day be synthesized.[63] Early corticotropin preparations were occasionally contaminated by minute quantities of other pituitary substances, particularly posterior pituitary fractions, but with recent advances in purification, contamination has been almost completely eliminated.[40] To humans, corticotropin derived from animal sources is a foreign protein, and sensitivity reactions, although uncommon, have been observed. Pyrogenic reactions, urticaria and contact dermatitis have been reported.[14, 52, 71, 125]

METHOD OF ASSAY

Corticotropin is assayed by an adrenal ascorbic acid depletion test devised by Sayers, Sayers and Woodbury, in comparison with a provisional U.S.P. standard.[1, 100] There is likely to be considerable variation in different batches of any substance which must be assayed by biologic methods. According to Mote, a statistical variation of less than 20 per cent in the Sayers and Sayers bioassay technique is considered good; variations of a greater magnitude are not uncommon.[77] Furthermore, all brands of corticotropin are not made by the same process and there are differences in stability, solubility and absorption rates.[1] These factors may occasionally be of clinical importance. Some patients who seem to be maintained satisfactorily on a certain dose of one kind of corticotropin have a different response if a similar amount of another preparation is given. Because of this variability in potency, it has been suggested that human assay may be superior to animal assay.[82, 91]

Cortisone, a pure crystalline substance of known chemical structure, is of course assayed by weight. During initial investigational studies, some variation was noted in the potency of various batches of cortisone. This was believed due to "unstable suspensions."[52] This difficulty was quickly overcome. The reviewer is not aware of any reports in the past two years of variability in the potency of different preparations of cortisone.

MODE OF ACTION OF CORTICOTROPIN

Corticotropin acts by stimulating the adrenal gland to increase the synthesis and discharge of adrenal steroids. Recent evidence indicates that Compound F of Kendall, or hydrocortisone, is the principal hormone that is elaborated by the stimulus of corticotropin, along with smaller amounts of corticosterone and cortisone.[20, 73, 79, 87] Cholesterol, present in high concentration in the adrenal cortex, is probably the precursor of these steroids. It might be supposed that corticotropin, by stimulating the secretion of several adrenal steroids, may produce clinical effects other than those derived from cortisone. There is little evidence to date, however, to support this supposition.[52]

A given quantity of corticotropin may elicit a variable response in adrenal steroidal output. An inactive gland, for instance, in a person with long-standing hypopituitarism may show a subnormal response to the same dose of the hormone which may produce a large output of adrenal steroids from a normally active gland.[64, 102] It is also possible that a gland which may be already greatly stimulated by endogenous corticotropin as a result, for instance, of stress, may respond subnormally to an administered dose of the hormone. However, the observa-

tions of Roche and his colleagues are not in accord with this.[95] They performed Thorn tests on patients in the postoperative period. In this group, the eosinophils were already depressed because of the stress induced by operation, yet when corticotropin was given a further depression of the eosinophils occurred. These findings would seem to indicate that the normal adrenal gland has a considerable reserve secretory power.

RESISTANCE TO CORTICOTROPIN

Resistance to corticotropin may develop, particularly in the course of long-term therapy. This may be manifest by a worsening of the symptoms and signs of the disease under treatment, and by a diminished eosinophil response to the Thorn test.[2] Holbrook and his associates noted that the dose of corticotropin required to control the symptoms and signs of rheumatoid arthritis progressively increased in 12 of 35 cases.[55] They observed three types of resistance: (1) Primary—in which there was no clinical response even the first time corticotropin was given. (2) Acquired species specific—in which after a satisfactory initial response, increasing doses of pig corticotropin were required to maintain a satisfactory response; on changing to beef corticotropin, a dramatic clinical response occurred with the same or smaller doses. (3) Acquired, apparent nonspecific—in which patients who required increasing amounts of pig corticotropin needed the same or larger doses of beef corticotropin. The cause of the development of this resistance is not known. Forsham and co-workers expressed belief it is due to tissue inactivation rather than to antihormone development.[39] It is noteworthy, however, that the resistance which develops following administration of other pituitary hormones, such as the thyrotropic, gonadotropic and diabetogenic hormones, is generally considered to be due to the development of a specific antihormone. A patient who becomes resistant to corticotropin administered intramuscularly usually is responsive to the hormone when it is administered intravenously. Thorn and his colleagues reported they had not encountered the development of resistance to purified corticotropin.[113]

METHODS OF ADMINISTRATION

Cortisone may be given orally, subcutaneously or intramuscularly. The onset of effect of cortisone given by mouth is usually more rapid and the duration of action shorter than when it is administered intramuscularly. The effect when it is given by mouth usually lasts six to eight hours; when given intramuscularly, from 24 to 48 hours.[13, 115] It is advisable, therefore, when the hormone is administered by mouth, to give it in divided doses. The effective oral dose in 100 cases of rheumatoid arthritis studied by Ward and colleagues was equal to the intramuscular dose in about one-half the cases; in the other half about a sixth to a quarter more of the preparation was required when it was given orally.[115] Cortisone is rarely ineffective orally.

The method of administration as well as the dose of corticotropin greatly influences the adrenal response. The hormone is ineffective if given orally, as it is inactivated by gastrointestinal enzymes. A single dose of corticotropin given intramuscularly will produce a measurable adrenal response within thirty minutes. This will be maximal in four hours and will disappear in approximately twelve hours.[40] For continuous therapeutic control throughout the 24-hour period, it has been necessary to give corticotropin in divided doses every six to eight hours.

To obviate the necessity of multiple daily injections, long-acting preparations for intramuscular use exclusively have been made by the addition of substances which delay absorption of corticotropin from the site of injection.[122, 123] Gelatin is the menstruum currently used in commercial preparations. Some investigators are skeptical as to whether the long-acting preparations, given once or twice daily, are as therapeutically effective as the aqueous preparations given at four- to six-hour intervals.[56] Thorn and associates, however, expressed the opinion that purified corticotropin in gelatin, which has a sustained effect on the adrenal cortex for longer than 24 hours, is a very effective therapeutic agent.

Gordon[47] observed that 50 mg. of corticotropin given by constant intravenous drip results in a much greater adrenal stimulation than does 100 mg. of the same preparation given intramuscularly in 25 mg. doses at six-hour intervals. In fact, as little as 10 mg. of corticotropin given intravenously daily for ten days has produced many of the signs and symptoms of Cushing's disease.[77] The observations of Renold and his colleagues indicate the importance of the time factor in intravenous administration.[92] Twenty milligrams of corticotropin given in one minute produces no significant adrenocortical activity; the same dose given over a period of two days will triple the daily excretion of 17-ketosteroid. Twenty milligrams seems to be a critical dose. Increasing the amount administered intravenously in an eight-hour period above this figure does not significantly increase the adrenocortical response.

CUSHING'S SYNDROME

Before corticotropin and cortisone were available in substantial quantities for clinical investigation, some knowledge as to their physiologic effects was accurately predicted by studies of the various manifestations of Cushing's syndrome.[107] The features of this syndrome are a characteristic adiposity, diminished carbohydrate tolerance, hypertension, nega-

tive nitrogen balance, lymphopenia and eosinopenia, osteoporosis, acne, cutaneous striae and hirsutism. There is an increased urinary excretion of adrenal hormones. Susceptibility to infection and poor wound healing also occur. Mental disturbances are not uncommon. Most if not all of these features have been produced with large doses of cortisone and corticotropin given over prolonged periods of time. It is important to emphasize, however, that the changes induced by the hormones are nearly always reversible and disappear with cessation of treatment or reduction of the dose.

EFFECTS ON WATER AND ELECTROLYTE METABOLISM

Cortisone and corticotropin may have varying effects on water metabolism. There may be either retention or diuresis during hormone administration, depending upon the preexisting physiologic state. Such alterations are usually a consequence of changing plasma electrolyte levels. At times, however, a dissociation may occur between urinary excretion of water and of electrolytes.[113] Soon after hormone administration is begun there is a transient shift of water, sodium and chloride into the extracellular spaces. This reaches a peak within 8 or 9 days and then subsides as treatment continues. Cortisone in daily doses of 100 mg. will cause little if any change in the balance of calcium, phosphorus, sodium, potassium and chloride, and in the concentration of these ions in the blood.[107] Corticotropin in 100 mg. daily doses intramuscularly and cortisone in 200 mg. daily doses will regularly induce a negative balance of potassium. The effects on excretion of sodium and chloride are somewhat variable. Usually there is early retention of the ions, followed later by increased excretion.

EFFECTS ON CARBOHYDRATE METABOLISM

In the doses usually employed, cortisone and corticotropin ordinarily do not produce alterations in carbohydrate tolerance. Sprague and associates noted no significant changes in the fasting blood sugar levels in 16 patients with rheumatoid arthritis under treatment with cortisone.[107] In 14 of these patients, glucose tolerance tests were performed. In 10, the results were normal; in 4, abnormal curves were observed. Two of the patients with abnormal glucose tolerance were tested after cessation of treatment and had normal tolerance curves. The occasional occurrence of diabetes mellitus has been reported in patients whose carbohydrate tolerance both before and after treatment was normal.[19] The insulin requirement of diabetic patients has been observed to increase during the administration of these hormones.[12]

EFFECTS ON FAT METABOLISM

The most evident effect of these hormones on fat metabolism is an alteration in fat deposition, with the appearance of moon-shaped facies and fatty deposits in the cervicodorsal and supraclavicular areas.[109] Hypercholesterolemia has been observed during prolonged treatment with corticotropin and cortisone.[3, 93]

EFFECTS ON NITROGEN METABOLISM

Although cortisone has been shown experimentally to inhibit protein synthesis and to increase protein catabolism, the effects of therapeutic doses of cortisone on nitrogen metabolism in man have not been striking. One hundred milligrams a day causes little or no augmentation in nitrogen excretion, but 200 mg. a day of cortisone and 100 mg. a day of corticotropin intramuscularly cause a negative nitrogen balance.[107] A significant increase in urinary excretion of uric acid and a decrease in uric acid content of serum have been observed with the administration of cortisone in 100 and 200 mg. doses and with 100 mg. doses of corticotropin. This is particularly evident when the content of uric acid in the serum before the hormones are given is in the upper part of the normal range or elevated.[107]

CARDIOVASCULAR EFFECTS

Blood Pressure: There has gradually accumulated a large amount of evidence linking the adrenal cortex with hypertension.[83] Hypertension is a common occurrence in Cushing's disease; contrariwise, hypotension is frequent in Addison's disease. There has been some variance of opinion as to the effects of corticotropin and cortisone in humans. In normotensive patients with normal renal function, Perera found no significant variation in blood pressure occurring during cortisone administration.[85, 86] Dustan and colleagues confirmed this with regard to cortisone.[31] Corticotropin, however, in 60 to 200 mg. daily doses intramuscularly, increased the blood pressure of both normotensive and hypertensive persons. Hein and Whipple noted that "about half" of a group of 22 patients receiving rather large doses of corticotropin and cortisone had elevation of systolic pressure of 30 mm. of mercury or more, and of diastolic pressure of 10 mm. or more.[50] In hypertensive patients, especially those with impaired renal function, a further increase in blood pressure seems to be a common although not invariable occurrence during hormone administration.[103] On the other hand, the administration of cortisone to children with the adrenogenital syndrome may result in a very significant reduction in blood pressure.[121]

Capillary Permeability: Increased capillary resistance as measured by a negative pressure method has

been noted after various types of stress. Robson and Duthie measured capillary resistance in patients under treatment with corticotropin and cortisone. In most, there was an increase in capillary resistance.[94] In two cases of idiopathic thrombocytopenic purpura, Robson and Duthie noted an increase in capillary resistance although there was no change in the number of platelets. However, Bethell and colleagues,[10] and Jacobsen and Sohier[59] observed increases in the number of platelets in the blood of patients with thrombocytopenic purpura who were receiving either substance. On the other hand, easy bruising, presumably related to increased capillary fragility, has been noted during prolonged hormone therapy.

Thromboembolic Complications: Cosgriff and associates[23] observed a considerable shortening of the coagulation time of venous blood in patients under treatment with these substances. The mechanism of this alteration is not clear but it seems to be of some clinical importance. The incidence of thromboembolic complications, particularly thrombophlebitis and pulmonary embolism, in patients under treatment with these hormones or during the first three or four weeks following treatment, seems to be higher than it might logically be expected to be from the underlying disease process alone.[24] Fahey, however, could not confirm Cosgriff's observations; he noted no significant alteration of the coagulation time after the administration of either hormone.[35]

RESPIRATORY EFFECTS

Cortisone and corticotropin increase the vital capacity and maximal breathing capacity in several chronic pulmonary diseases, including bronchial asthma, emphysema, beryllium granulomatosis, silicosis and sarcoidosis. Investigation of these effects has been limited and the results have not been completely consistent.[44, 61, 117]

GASTROINTESTINAL EFFECTS

Gastric Secretion: Gray and associates[48] studied the effect of corticotropin on gastrointestinal enzymes and of cortisone and corticotropin on gastric secretion. They demonstrated that these substances cause an increase of about 200 per cent in basal and nocturnal secretion of acid and pepsin. In every instance, corticotropin increased the acid secretion to an amount usually associated with active duodenal ulcer. Similar gastric response may be brought about by cortisone. One patient under their observation who had been given cortisone had two perforated duodenal ulcers, a second a massive fatal gastrointestinal hemorrhage, and a third a massive gastrointestinal hemorrhage and duodenal perforation. The occurrence of such untoward complications has been confirmed by many investigators.

HEMOPOIETIC EFFECTS

Both cortisone and corticotropin may cause neutrophilic leukocytosis for short periods, and both bring about eosinopenia and lymphopenia.[114] With corticotropin, eosinopenia may continue as long as the hormone is given and for some weeks thereafter, or there may be a return to near normal levels even while corticotropin therapy continues. During prolonged administration of cortisone, a significant increase in circulating neurophils has been observed, but no significant decrease in lymphocytes and eosinophils occurs.[107] The prompt eosinopenic response to corticotropin has been utilized by Thorn as a test for adrenocortical function. Although it may be inaccurate in certain circumstances, it remains the simplest method of estimating adrenocortical function.[112] Reticulocytosis and increase in the number of erythrocytes may follow hormone therapy of several diseases in which anemia is present.[36]

EFFECTS ON ENDOCRINE GLANDS

Pituitary: Corticotropin and cortisone both inhibit anterior pituitary function. Cytologic changes, similar to those that occur in spontaneous Cushing's disease, have been noted in the pituitary gland in patients to whom the hormones were given.[65] It is believed by some investigators that these alterations are retrogressive in nature and are secondary to increased circulating adrenal hormones. Recently, Sayers and co-workers demonstrated diminished content of corticotropin in the blood of patients with adrenogenital syndrome who received cortisone.[113] Ingle,[58] in 1938, demonstrated that adrenal atrophy which developed in rats following cortin administration is a consequence of depression of adrenotropic function of the anterior pituitary. Evidence of pituitary depression may, therefore, be indirectly derived through determination of adrenocortical function, which can be more easily estimated than can pituitary function.

Adrenal: Corticotropin causes an increase in the size of the adrenal cortex. Histologically, a loss of fat and hypertrophy of the zona reticularis and the zona fasciculata occur. Cortisone causes a definite decrease in the size of the adrenal cortex. Pronounced atrophy of the zona reticularis and of the zona fasciculata has been observed.[81] Alterations in secretory activity parallel these anatomic changes. Corticotropin brings about prompt increase in the urinary excretion of both 17-ketosteroids and corticosteroids. Cortisone usually causes a decrease in the urinary secretion of 17-ketosteroids initially, followed by a gradual leveling off with continued treat-

ment. Corticosteroid excretion usually increases when cortisone is administered; with prolonged treatment, this usually levels off, but remains above the pretreatment levels.[107, 114]

Adrenal Insufficiency on Hormone Withdrawal: Following withdrawal of either of these substances, there may be a period of adrenocortical insufficiency of variable degree, which may last for a few days to as long as three months. This is usually more pronounced after cortisone treatment, but also occurs following corticotropin administration. It may be manifested clinically by asthenia, somnolence, anorexia or depression. The urinary excretion of adrenocortical hormones decreases sharply and there is a diminished response to the Thorn test.[108] Eliel and associates,[33] in studies of water and electrolyte changes following discontinuation of these hormones, observed substantial losses of sodium and chloride after both, indicative of adrenocortical suppression. For instance, one patient after receiving 100 mg. of corticotropin per day for 30 days, lost two and one-half times as much sodium and five times as much chloride as was retained during the period of hormone administration. This temporary period of adrenal suppression, although at times distressing to the patient, may be of little serious consequence. However, if during this period the patient should be subjected to the stress of a serious injury, operation or illness, the adrenal response might prove inadequate. Fatalities have occurred in cases in which cortisone was discontinued immediately before a surgical operation.[42] To avoid iatrogenic adrenal insufficiency, administration of cortisone should never be halted abruptly, but decreased gradually over a period of several weeks.

Thyroid: Depression of thyroid function has been observed in patients under treatment with both corticotropin and cortisone. There is a reduction in the uptake of radioactive iodine (I^{131}) by the thyroid gland and by a low serum protein-bound iodine. The basal metabolic rate is reduced to minus 15 per cent or lower in only one-third of the cases. The reason for this is that corticotropin and cortisone are both calorigenic; both increase basal oxygen consumption in man by a direct action which does not involve alterations in thyroid function. Thyroid depression during hormone treatment may, therefore, be more pronounced than the basal metabolic rate indicates.[53, 124]

ANDROGENIC EFFECTS

Hirsutism in female patients is a common complication of long-term cortisone and corticotropin therapy.[52, 97] Acne occasionally occurs, particularly in younger patients. It is believed that these changes are related to the androgenic activity of the adrenal hormones. Fortunately, other evidences of masculinization do not occur. The hirsutism is usually mild, consisting of a light growth of hair on the upper lip and chin and along the cheeks. Nevertheless, to some patients this has been the most objectionable complication of therapy with these hormones.

NEUROLOGIC AND PSYCHIATRIC EFFECTS

Convulsive Seizures: The electroencephalograms of patients with epilepsy may become more abnormal during cortisone therapy.[46] Also, abnormal changes have been noted in encephalograms of patients who previously had normal tracings, indicating that both corticotropin and cortisone influence electrical activity of the brain.[54] Further evidence of increased cerebral excitation is suggested by reports of convulsions in patients without a previous history of seizures.[30]

Psychiatric Disturbances: Mental disturbances are frequent complications of treatment with either hormone. Most common are mild deviations of mood, particularly euphoria, generally regarded by both patient and and physician as a beneficial effect. However, psychoneurotic responses and frank and alarming psychoses may also occur. Rome and Braceland[96] expressed belief that psychotic reactions will develop in patients who have made only marginal psychological adjustment in the past.[96] This has not, however, been the experience of Clark, Bauer and Cobb.[16] In reviewing their observations of major mental disturbances during cortisone and corticotropin therapy, they noted that none of their patients who became mentally or emotionally disturbed while on treatment had a history of major mental disease. Furthermore, systematic clinical study revealed no clue to enable them to anticipate the occurrence of psychiatric complications. They stressed the importance of close observation for the early detection of these mental disturbances. Some of the premonitory signs which have been noted include paresthesias in the frontal region of the forehead (usually described as a sense of heaviness, fullness or fuzziness), insomnia, restlessness and agitation in some, lethargy and apathy in others. Delusional ideas and frank psychotic behavior may be the initial symptoms. It may be noted that all ten of the patients reported upon by Clark, Bauer and Cobb were receiving moderately large doses of corticotropin. As yet, no correlation has been established between any metabolic change induced by these hormones and development of mental disturbances.

OSTEOPOROSIS

Osteoporosis is a common manifestation in Cushing's disease. As might be expected, it has also developed in the hyperadrenal state induced by corti-

cotropin and cortisone. It is difficult, nevertheless, to determine the actual potency of these hormones as osteoporosis-producing agents. First of all, comparisons of roentgenograms taken at various intervals in treatment are unsatisfactory due to variations in radiographic technique; secondly, many of the patients who have received these hormones had a considerable degree of osteoporosis before treatment was begun. For instance, in the five female patients treated for long periods with cortisone by DiMartini and associates,[28] who developed pathologic fractures, one or more factors commonly predisposing to osteoporosis were present. These were prolonged bed-rest, an active disease process and the postmenopausal state. That cortisone does not always have a deleterious effect on bone metabolism is suggested by the following case report of Thorn and co-workers: A 51-year-old woman with non-tropical sprue of 13 years' duration and severe, generalized osteomalacia, had bilateral, impacted, subcapital fractures of the femoral neck as the result of a fall. Despite the presence of severe bone disease, cortisone in 100 mg. daily doses was continued for a month and then at 50 mg. daily thereafter. There was considerable improvement in the patient's health and weight. Although there had been complete absence of healing during a period of five weeks prior to cortisone therapy, both fractures healed satisfactorily, and three months after bilateral hip nailing, no distinct fracture line was evident.[113]

EFFECTS ON WOUND HEALING

Ragan and associates were the first to point out that corticotropin and cortisone may retard wound healing, both in humans and experimental animals.[90] Similar findings were noted by Alrich and associates[4] in rats, and by Spain and co-workers[104] in mice that were pretreated with corticotropin and cortisone. The doses used by these investigators were proportionally much larger than those commonly employed clinically. Cole and associates[17] noted no retardation of wound healing in dogs given these hormones in proportionally smaller doses. Poor wound healing, as has been mentioned before, is a fairly common occurrence in Cushing's disease, and there have been several references in the literature to this occurrence in patients receiving corticotropin and cortisone. In some cases it was not clear whether it was owing to the therapy or to underlying disease. Rosenberg and associates,[97] for instance, mentioned 20 patients who had skin and muscle biopsies just before corticotropin treatment. In 16, the wound healed promptly; in 4, there was a delay in wound healing, but 3 of the 4 had a generalized inflammatory disease of the skin. Other observers[49, 52] have noted no delay in wound healing. Ford and Key, for example, observed no interference with wound healing following orthopedic operations in 20 patients who were receiving cortisone, generally in smaller than ordinary doses and for relatively short periods.[41] The experimental studies of Findlay and Howes may help to explain these divergent reports.[37] They studied the combined effect of cortisone and partial protein depletion in wound healing in rabbits. When 1.5 mg. of cortisone per kilogram of body weight was given to rabbits on a normal diet, only a slight delay in wound healing was noted. A similar retardation was noted in animals depleted of protein but not receiving cortisone. However, the administration of cortisone to protein-depleted rabbits caused serious delay in wound healing. Many of the cortisone-treated patients in whom this complication developed had chronic febrile diseases. Protein depletion undoubtedly occurs in such cases and may well have been a factor in prolonged wound healing.

EFFECTS ON BACTERIAL INFECTIONS

Cortisone and corticotropin may bring about defervescence and apparent clinical improvement in patients with bacterial infections even though bacteremia may still be present. Considerable experimental evidence indicates the hormones cause lessening of resistance to bacterial infections. Experimental infection of cortisone-treated rabbits with streptococci and of cortisone-treated rats with tubercle bacilli caused the death of the animals, whereas in untreated animals that were given the same doses of the organisms there were no demonstrable systemic effects.[75, 76] The Committee of Medical Research of the American Trudeau Society has recommended that these drugs not be used in patients with active tuberculosis, and used only with extreme caution in patients with possible latent tuberculosis.[7] It is the committee's recommendation that diagnostic examinations for tuberculosis be carried out on all patients in whom the use of these hormones is contemplated. Not only have cortisone and corticotropin been inculpated in the reactivation of old and apparently arrested tuberculosis, but several fulminating and fatal cases have been reported in which the x-ray films of the chest before treatment were considered normal.[43, 62] Recently, the Committee on Therapy of the American Trudeau Society reviewed the cases of 81 patients with tuberculosis who had received either cortisone or corticotropin or both. In 40 cases the course of the disease was unfavorable, in 10 favorable, and in 25 apparently not changed. The committee surmised that "a large number of cases with unsuspected tuberculous disease must have received these hormones without harmful

effect," and it concluded that reactivation of tuberculous infection does not invariably result from treatment with cortisone or corticotropin.[18]

ANTIPHLOGISTIC EFFECTS

That cortisone and corticotropin suppress inflammation has been amply documented by observations in a wide variety of diseases, particularly in the fields of arthritis, dermatology, ophthalmology, allergy and cardiology. Careful histologic studies indicated that all elements of inflammatory response to a variety of etiologic agents may be suppressed by these hormones; that vascular tone is better maintained and there is less endothelial damage; that diapedesis of leukocytes is consequently lessened and there is a reduction of exudate; and that margination or "walling-off" of the area of injury by cellular elements is diminished.[32, 74, 105]

Because of the evidence linking the adrenal cortex with inflammation, it is suggested that the hormone may suppress inflammation by interfering in some manner with antigen-antibody reaction.[118, 119] This problem has been investigated at great length, but the results have not been altogether consistent. It is generally agreed, however, that corticotropin and cortisone do not interfere with antigen-antibody union, although they may inhibit the development of antibodies. Fischel[38] and Daugherty[26, 27] expressed doubt that inhibition of antibody formation is an adequate explanation for the anti-inflammatory properties of the hormones, for the amount of corticotropin required for complete suppression of circulating antibodies is far greater than that required to diminish allergic inflammation. Daugherty[27] concluded that cortisone diminishes inflammatory response to traumatic, bacterial and chemical as well as to allergic stimuli, not through some mechanism related to antigen-antibody union, but rather by a "specific antiphlogogenic action of its own." Although this cannot be accepted as a final answer, it seems to be a reasonable working hypothesis until knowledge of the manifold actions of these hormones is more complete. Precise information is still lacking, but the locus of the inflammatory action of the hormones is probably the tissue cell. Corticotropin and cortisone do not destroy or inhibit etiologic agents, but they so alter cellular physiology that the tissues are unable to sustain an inflammatory response. It is important to note that these hormones suppress both "useful and useless" inflammation with impartiality. The suppression of inflammatory response to bacterial infection is, of course, undesirable; the inhibition of the apparently useless inflammatory response of rheumatoid arthritis or a non-specific iritis is very desirable.

INCIDENCE AND IMPORTANCE OF UNDESIRABLE EFFECTS

How often do undesirable physiological effects occur? The overall incidence in several large series, including many cases in which treatment was continued over a long term, has been between 40 per cent and 66 per cent.[11,97,110,111] It is important to emphasize that many of these undesirable reactions are of little consequence and do not interfere with treatment. In none of 100 carefully selected cases of rheumatoid arthritis in which Ward and co-workers administered cortisone therapy was it necessary to discontinue treatment because of side effects; in only 10 per cent to 20 per cent of cases in which long-term treatment was given have such effects forced discontinuation of treatment.[67, 115, 116] To avoid these reactions or keep them to a minimum it has been frequently necessary for the clinician to strike a compromise between desired therapeutic result and adverse reactions by using amounts of these hormones which only partially suppress the disease process under treatment. It is pertinent to note at this time that the incidence of side effects is influenced by the daily dose employed and the sex of the patients. In the experience of Ward and co-workers,[115] side effects occurred in 63 per cent of patient receiving 75 mg. a day, compared with only 12 per cent in those receiving less than 75 mg. daily. Among patients receiving 75 mg. daily, side effects developed in 50 per cent of the men, in 72 per cent of the premenopausal women and in 85 per cent of the postmenopausal women.

Copeman[21] noted a tendency to attach undue importance to mild side effects: "The preoccupation of many observers to mild side effects reminds one of a house-proud woman over-conscious of a speck of dust which the visitor has not noticed." It is certainly true that the adverse reactions from these hormones have received very wide publicity in countless case reports, reviews and even monographs.[20, 111] Such reports may have partially obscured the numerous cases in which these hormones have been employed successfully. In some instances they have been life-saving; in others they have restored invalids and semi-invalids to a much happier, useful state. The use of any potent medication carries with it a calculated risk. After four years of clinical trial, it seems evident, nevertheless, that physicians who have some understanding of the protean actions of cortisone and corticotropin and who accordingly select patients and observe them carefully, can employ the hormones with great advantage and small risk.

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REFERENCES

The full list of 125 references may be obtained from the author.